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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/576,989	05/23/2000	Charles M. Rice III	6029-4356	1745

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EXAMINER	
BRUMBACK, BRENDA G	
ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 01/10/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/576,989	RICE ET AL.	
	Examiner	Art Unit	
	Brenda G. Brumback	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 December 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-24,29,41-44,61-70 and 72-75* is/are pending in the application.

4a) Of the above claim(s) *18-24,41-44 and 63-68* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3-17, 29, 61-62, and 69-70 and 72-75* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *2&3* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group I (claims 1, 2-17, 61-75 and claims 25-40 and 45-60 in part) in Paper #7 is acknowledged. Applicant's request to rejoin Group II with Group I and examination of all pending claims due to cancellation of claims 2, 25-40, 45—60, and 71 and incorporation of the limitation of claim 2 into claim 1 is not found persuasive because Group I is drawn to polynucleotides comprising an NS5A gene mutation and Group II is drawn to polynucleotides comprising a foreign IRES/gene. The polynucleotides of Group II have a different and distinct structure from the polynucleotides of Group I, and would thus require a separate and additional search. For this reason, examination of all pending claims together would constitute an undue burden.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 1, 3, 7, 9-10, 29 and 65 have been amended. Claims 2, 25-28, 30-40, 45-60, 71, and 76-85 have been canceled. Claims 1, 3-24, 29, 41-44, 61-70, and 72-75 are pending. Claims 18-24, 41-44, and 63-68 are withdrawn from consideration as directed to a nonelected invention. Claims 1, 3-17, 29, 61-62, 69-70, and 72-75 are examined on the merits to the extent that they read on the elected group, polynucleotides comprising a non-naturally occurring HCV sequence comprising an NS5A gene mutation capable of productive replication in a host cell.

The Supplemental Amendment filed 12/10/2001 amending claim 1 is acknowledged.

Priority

3. It is noted that the present application is a continuation-in-part of parent application SN 09/034,756 filed 03/04/1998, which application claims priority to Parent Application SN 08/811,566 and Provisional Application SN 60/039,843. Upon review, while the parent applications provide support for polynucleotides comprising a non-naturally occurring HCV sequence capable of productive replication in a host cell, these applications do not appear to provide support for the presently claimed invention drawn to polynucleotides comprising a non-naturally occurring HCV sequence capable of productive replication in a host cell which further comprises an NS5A gene adaptive mutation. Therefore, for purposes of examination, the priority date of the present application has been determined to be the same as the filing date of the present application, 05/23/2000. Applicant may receive the benefit of the filing date of one or more of the earlier applications by pointing out where specifically in the specification of the parent application(s) support can be found for an adaptive mutation which is an NS5A gene mutation

Drawings

4. The Formal Drawings filed 12/04/2000 are acknowledged.

Information Disclosure Statement

5. The Information Disclosure Statements filed 09/07/2000 (Paper #2) and 09/11/2000 (Paper #3) are acknowledged. Signed copies are attached hereto.

Please note: Because no copies of the Foreign Documents were provided with the IDS filed 09/07/2000, those documents which could not be accessed were not considered. For consideration of documents BV and CG, applicant must submit a copy of the document and a concise explanation of the relevance, as it is presently understood by the individual designated in 37 CFR 1.56(c) most knowledgeable about the content of the information, if the patent listed is not in the English language.

Specification

6. An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification. The present application should be amended to reference parent application 09/034,756 and its current status.

The specification is objected to as containing hyperlinks and/or other forms of browser-executable code embedded in the text of the patent application, which are impermissible (see page 2, line 19 of the disclosure). The attempt to incorporate subject matter into the patent application by reference to a hyperlink and/or other forms of browser-executable code is considered to be an improper incorporation by reference.

See MPEP 608.01(p), paragraph I regarding incorporation by reference. Applicant is required to delete the browser-executable code.

Claim Rejections - 35 USC § 112

7. Claims 1, 3-9, 12-17, 29, 61-62, and 69-75 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites a polynucleotide comprising an adaptive mutation. The specification discloses adaptive mutations as encompassing mutations which render the polynucleotide capable of replication in a non-hepatic cell or which cause the polynucleotide to have attenuated virulence. The specification discloses mutations of the NS5A gene (page 12, line 23, through page 13, line 6, and page 61, line 24, through page 62, line 16) but fails to disclose what other adaptive mutations are encompassed within the claimed invention. Absent such disclosure, the metes and bounds of the claimed invention cannot be determined and the claims are indefinite.

Claims 12-13 and 15-16 recite an "ISDR". For clarification of the claims, it is suggested that the full name of the phrase abbreviated as "ISDR" be written out at the first occurrence in the claims, *i.e.*, interferon sensitivity determining region (ISDR).

Claim 70 depends from claim 2, which has been canceled. Claim 72 depends from claim 71, which has also been canceled. The metes and bounds of claims which depend from canceled claims cannot be determined and thus, the claims are indefinite.

For purposes of examination, the claims have been interpreted as depending from claims 1 and 70 respectively. Clarification and correction are required.

8. Claims 1-9, 29, 61-62, and 69-75 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a polynucleotide comprising a non-naturally occurring HCV sequence capable of production in a host cell and further comprising an adaptive mutation of the NS5A gene, does not reasonably provide enablement for a polynucleotide comprising a non-naturally occurring HCV sequence capable of production in a host cell and further comprising an adaptive mutation other than a mutation of the NS5A gene. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The first paragraph of 35 U.S.C. 112 states, "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same...". The courts have interpreted this to mean that the specification must enable one skilled in the art to make and use the invention without undue experimentation. The courts have further interpreted undue experimentation as requiring "ingenuity beyond that to be expected of one of ordinary skill in the art" (Fields v. Conover, 170 USPQ 276 (CCPA 1971)) or requiring an extended period of experimentation in the absence of sufficient direction or guidance (In re Colianni, 195 USPQ 150 (CCPA 1977)).

Additionally, the courts have determined that "... where a statement is, on its face, contrary to generally accepted scientific principles", a rejection for failure to teach how to make and/or use is proper (In re Marzocchi, 169 USPQ 367 (CCPA 1971). Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Colianni, 195 USPQ 150, 153 (CCPA 1977) and have been clarified by the Board of Patent Appeals and Interferences in Ex parte Forman, 230 USPQ 546 (BPAI 1986). Among the factors are the nature of the invention, the state of the prior art, the predictability or lack thereof in the art, the amount of direction or guidance present, the presence or absence of working examples, the breadth of the claims, and the quantity of experimentation needed. The instant disclosure fails to meet the enablement requirement for the following reasons:

The nature of the invention: The claimed invention is drawn to a polynucleotide comprising a non-naturally occurring HCV sequence that is capable of productive replication in a host cell and further comprising an adaptive mutation. Although the metes and bounds of the recited adaptive mutation are indefinite for the reasons outlined *supra*, the adaptive mutation has been interpreted for examination purposes as encompassing any and all mutations which render the polynucleotide capable of replication in a non-hepatic cell or which cause the polynucleotide to have attenuated virulence.

The state of the prior art and the predictability or lack thereof in the art: The art teaches that adaptive mutations which can be made to HCV polynucleotides without

rendering the polynucleotide incapable of productive replication in a host cell are unpredictable. Yanagi et al. (U.S. Patent 6,153,421, see column 8, lines 26-32, and column 120, claim 22) teach that such adaptive mutations are limited to deletion of part or all of the polynucleotide portions encoding the P7, NS4B, or NS5A protein.

The amount of direction or guidance present and the presence or absence of working examples: The specification discloses how to make adaptive mutations in the NS5A gene which render the virus capable of productive infection in Huh7 cells (see page 12, line 23, through page 13, line 6 and pages 61-62). The specification does not disclose other adaptive mutations which can be made without rendering the polynucleotide incapable of productive replication in a host cell.

The breadth of the claims and the quantity of experimentation needed: Because of the teachings of unpredictability found in the art regarding adaptive mutations in genes other than the P7, NS4B and NS5A without loss of the ability for productive replication in a host cell and because applicant's specification fails to disclose additional adaptive mutations which can be made without loss of the ability for productive replication, it would require undue experimentation by one of skill in the art to be able to practice the claimed invention commensurate in scope with the claims.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –

> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 1, 7, 9-11, 61-62, 69-70, 72 and 73-74 are rejected under 35 U.S.C. 102(e) as being anticipated by Yanagi et al.

The claimed invention is drawn to a polynucleotide (double stranded DNA) comprising a non-naturally occurring HCV sequence that is capable of productive replication in a host cell, wherein the HCV comprises a functional 5' non-translated region, one or more protein coding regions, a functional 3' non-translated region and either an adaptive mutation of the NS5A gene or an attenuating mutation. The claimed invention is also drawn to a vector comprising the polynucleotide operably associated with a promoter, a host cell comprising the vector, and a host cell which is a human liver cell, T-cell or B-cell. As was outlined *supra*, absent evidence that the claimed adaptive mutation of the NS5A gene enjoys support in parent applications prior to the filing date of the present application, the priority date for the claims under examination has been determined to be 05/23/2000 for purposes of examination on the merits.

Yanagi et al. teach isolated and purified polynucleotides (cDNA molecules) which are capable of productive replication in a host cell and which comprise a

functional 5' non-translated region, one or more protein coding regions, and a functional 3' non-translated region (see column 4, lines 41-42; column 6, lines 8-21; and column 28, lines 43-50). Yanagi et al. teach an embodiment of the polypeptides in which part or all of the portion of the polynucleotide encoding the NS5A protein is deleted (see column 8, lines 26-38, and column 120, claim 22). Yanagi et al. teach that deletions in the polynucleotides encoding the infectious nucleic acid sequences may be made in order to produce attenuated HCV for vaccine development (see column 3, lines 15-28). Yanagi et al. teach vectors comprising the polynucleotides operably linked to a promoter (see column 9, line 47, through column 10, line 6). Yanagi et al. teach suitable host cells for culturing HCV as comprising hepatocytes and lymphocytes (see page 9, lines 15-17).

Claim Rejections - 35 USC § 102/103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

a. Claims 3-6 and 29 are rejected under 35 U.S.C. 102(e) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Yanagi.

The claimed invention is as described *supra*, wherein the transfection efficiency into mammalian cells is greater than 0.1%, 1%, or 5%, or is about 6%. Yanagi et al. teach polynucleotides as described *supra*. While Yanagi et al. are silent as to the transfection efficiency of the polynucleotides into mammalian cells, absent some evidence to the contrary, polynucleotides having the recited structure of a functional 5' non-translated region, one or more protein coding regions, a functional 3' non-translated region and a deletion of a portion or all of the NS5A protein would inherently possess a transfection efficiency into mammalian cells of greater than 0.1%, 1%, or 5%, or about 6%.

b. Claims 12-13 and 15-16 are rejected under 35 U.S.C. 102(e) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Yanagi et al. in light of Gale et al (Virology, 230/2:217-27, April 1997).

The claimed invention is drawn to a polynucleotide comprising a non-naturally occurring HCV sequence that is capable of productive replication in a host cell, wherein the HCV comprises a functional 5' non-translated region, one or more protein coding regions, a functional 3' non-translated region and an adaptive mutation of the NS5A gene near or including part or all of the ISDR.

Yanagi et al. a polynucleotide comprising a non-naturally occurring HCV sequence that is capable of productive replication in a host cell, with an adaptive mutation of the NS5A gene, as was set forth above. Gale et al. teach that the NS5A gene comprises the ISDR (see the abstract). The polynucleotide disclosed by Yanagi et

al., in which all of the NS5A gene has been deleted, would inherently comprise a deletion of the ISDR.

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 8 and 75 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yanagi et al. in view of Mizuno et al. (Gastroenterology 109/6:1933-40, December 1995).

The claimed invention is drawn to a HeLa host cell comprising a polynucleotide comprising a non-naturally occurring HCV sequence that is capable of productive replication in a host cell, wherein the HCV comprises a functional 5' non-translated region, one or more protein coding regions, a functional 3' non-translated region and an adaptive mutation of the NS5A gene.

Yanagi et al. teach comprising a polynucleotide comprising a non-naturally occurring HCV sequence that is capable of productive replication in a host cell, as set forth above. Yanagi et al. teach host cells comprising the polynucleotide, but do not teach the host cells as HeLa cells.

Mizuno et al. teach that HeLa cells can be transfected with HCV polynucleotides, producing virion-like structures (see the abstract).

One of ordinary skill in the art at the time the invention was made would have found it *prima facie* obvious to have transfected the polynucleotides disclosed by Yanagi et al. into the host cells described by Mizuno et al. as a convenient means of producing virions in a readily available cell line.

Double Patenting

12. A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claims 69-73 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 95-97 of copending Application No. 09/917,563. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are drawn to hepatocytes or human liver host cells comprising polynucleotides comprising a non-naturally occurring HCV sequence capable of producing infectious HCV and comprising an adaptive mutation.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

13. Claims 14 and 17 are free of the prior art.

14. No claims are allowed.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brenda Brumback whose telephone number is (703) 306-3220. If the examiner can not be reached, inquiries can be directed to Supervisory Patent Examiner Anthony Caputa whose telephone number is (703) 308-3995. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Examiner Brenda Brumback, Art Unit 1642 and should be marked "OFFICIAL" for entry into prosecution history or "DRAFT" for consideration by the examiner without entry. The Official FAX telephone number is (703) 872-9306 and the After Final FAX telephone number is (703) 872-9307. FAX machines will be available to receive transmissions 24 hours a day. In compliance with 1096 OG 30, the filing date accorded to each OFFICIAL fax transmission will be determined by the FAX machine's stamped date found on the last page of the transmission, unless that date is a Saturday, Sunday or Federal Holiday with the District of Columbia, in which case the OFFICIAL date of receipt will be the next business day.

Brenda Brumback
Patent Examiner